

Gain of Function Research

Gain of Function Research

Certain gain-of-function studies with the potential to enhance the pathogenicity or transmissibility of potential pandemic pathogens (PPPs) have raised biosafety and biosecurity concerns, including the potential dual use risks associated with the misuse of the information or products resulting from such research.

On October 16, 2014, the White House Office of Science and Technology Policy announced the launch of the U.S. Government (USG) gain-of-function (GOF) deliberative process to re-evaluate the potential risks and benefits associated with certain GOF experiments. During this process the USG paused the release of federal funding for GOF studies anticipated to enhance the pathogenicity or transmissibility among mammals by respiratory droplets of influenza, MERS, or SARS viruses.

The NSABB served as the official federal advisory body on the GOF issue and was tasked with providing recommendations to the USG on a conceptual approach for evaluating proposed GOF research. The NSABB finalized its recommendations on May 24, 2016. The U.S. Government considered the NSABB's findings and recommendations during the development of policy on gain-of-function research. In January 2017, the U.S. Government released policy guidance for the review and oversight of research anticipated to create, transfer, or use enhanced PPPs.

Department of Health and Human Services P3CO Framework

[Department of Health and Human Services Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens](#)

U.S. Government Policy on Enhanced PPP Research

[Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight](#)

U.S. Government Gain-of-function Deliberative Process

[NSABB Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research](#)

[U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses](#)

[FAQs on the U.S. government Gain-of-function Deliberative Process and Research Funding Pause](#)

Symposia Summaries and Commissioned Reports

[1st National Academies Symposium Summary \(December 15-16, 2014\) – Potential Risks and Benefits of Gain-of-Function Research: Summary of a Workshop](#)

[2nd National Academies Symposium Summary \(March 10-11, 2016\) – Gain-of-Function Research: Summary of the Second Symposium](#)

[Risk and Benefit Analysis of Gain of Function Research – Final Report \(Gryphon Scientific\)](#)

[Gain-of-Function Research: Ethical Analysis \(Professor Michael J. Selgelid\)](#)

Additional Material

[NIH Director's Statement on Funding Pause on Certain Types of Gain-of-Function Research](#)

[NIH Director's Statement on Lifting of NIH Funding Pause on Gain-of-Function Research](#)

[NIH Director's Statement on NIH's commitment to transparency on research involving potential pandemic pathogens](#)

[Supplemental Information on the Risk and Benefit Analysis of Gain-of-Function Research](#)

[Gain-of-Function Deliberative Process Written Public Comments \(Nov 10, 2014 – June 8, 2016\)](#)

External Resources

[S3: Science, Safety, and Security](#)

Biosafety, Biosecurity, and Emerging Biotechnology

[Biosafety and Recombinant DNA Policy](#)

[Biosecurity Policy](#)

[Emerging Biotechnology Policy](#)

NIH's GOF Definition [Archived]

SOLICITATION/CONTRACT/ORDER FOR COMMERCIAL ITEMS OFFEROR TO COMPLETE BLOCKS 12, 17, 23, 24, AND 30			1. REQUISITION NUMBER 0011533611-0001		PAGE 1 OF 44						
2. CONTRACT NO. W911QY20CD101		3. AWARD/EFFECTIVE DATE 17-Aug-2020		4. ORDER NUMBER		5. SOLICITATION NUMBER		6. SOLICITATION ISSUE DATE			
7. FOR SOLICITATION INFORMATION CALL:		a. NAME			b. TELEPHONE NUMBER (No Collect Calls)			8. OFFER DUE DATE/LOCAL TIME			
9. ISSUED BY W6QK ACC-APG NATICK CONTRACTING DIVISION BLDG 1 GENERAL GREENE AVENUE NATICK MA 01760-5011 TEL: FAX: 508-233-5700		CODE W911QY		10. THIS ACQUISITION IS <input type="checkbox"/> UNRESTRICTED OR <input checked="" type="checkbox"/> SET ASIDE: 100 % FOR: <input checked="" type="checkbox"/> SMALL BUSINESS <input type="checkbox"/> WOMEN-OWNED SMALL BUSINESS (WOSB) ELIGIBLE UNDER THE WOMEN-OWNED SMALL BUSINESS PROGRAM <input type="checkbox"/> HUBZONE SMALL BUSINESS <input type="checkbox"/> EDWOSB NAICS: 325412 <input type="checkbox"/> SERVICE-DISABLED VETERAN-OWNED SMALL BUSINESS <input type="checkbox"/> 8(A) SIZE STANDARD: 1,250							
11. DELIVERY FOR FOB DESTINATION UNLESS BLOCK IS MARKED <input type="checkbox"/> SEE SCHEDULE		12. DISCOUNT TERMS Net 30 Days		13a. THIS CONTRACT IS A RATED ORDER UNDER DPAS (15 CFR 700) <input type="checkbox"/>		13b. RATING					
15. DELIVER TO BARDAB (b) (6) BIOMEDICAL ADVANCED RESEARCH DEVELOPMENT AUTH 200 C STREET, SW WASHINGTON DC 20024		CODE W56XNH		16. ADMINISTERED BY CODE SEE ITEM 9							
17a. CONTRACTOR/OFFEROR OLOGY BIOSERVICES, INC NANOTHERAPEUTICS 13200 NW NANO COURT ALACHUA FL 32615-8726 TELEPHONE NO. 386-462-9663		CODE 3GQS9 FACILITY CODE 3GQS9		18a. PAYMENT WILL BE MADE BY CODE HQ0490 DEFENSE FINANCE AND ACCOUNTING SERVICE DIFAS-INDY VP GFEB5 8899 E 56TH STREET INDIANAPOLIS IN 46249-3800							
17b. CHECK IF REMITTANCE IS DIFFERENT AND PUT SUCH ADDRESS IN OFFER <input type="checkbox"/>		18b. SUBMIT INVOICES TO ADDRESS SHOWN IN BLOCK 18a. UNLESS BLOCK BELOW IS CHECKED <input checked="" type="checkbox"/> SEE ADDENDUM									
19. ITEM NO.		20. SCHEDULE OF SUPPLIES/ SERVICES		21. QUANTITY		22. UNIT		23. UNIT PRICE		24. AMOUNT	
		SEE SCHEDULE									
25. ACCOUNTING AND APPROPRIATION DATA See Schedule						26. TOTAL AWARD AMOUNT (For Govt. Use Only) (b) (4)					
27a. SOLICITATION INCORPORATES BY REFERENCE FAR 52.212-1, 52.212-4, FAR 52.212-3, 52.212-5 ARE ATTACHED. ADDENDA <input type="checkbox"/> ARE <input type="checkbox"/> ARE NOT ATTACHED											
27b. CONTRACT/PURCHASE ORDER INCORPORATES BY REFERENCE FAR 52.212-4, FAR 52.212-5 IS ATTACHED. ADDENDA <input type="checkbox"/> ARE <input type="checkbox"/> ARE NOT ATTACHED											
28. CONTRACTOR IS REQUIRED TO SIGN THIS DOCUMENT AND RETURN 1 COPIES TO ISSUING OFFICE. CONTRACTOR AGREES TO FURNISH AND DELIVER ALL ITEMS SET FORTH OR OTHERWISE IDENTIFIED ABOVE AND ON ANY ADDITIONAL SHEETS SUBJECT TO THE TERMS AND CONDITIONS SPECIFIED. REF: Recession of SARS-COV2 Fill				29. AWARD OF CONTRACT; REF. OFFER DATED 31-Jul-2020. YOUR OFFER ON SOLICITATION (BLOCK 5), INCLUDING ANY ADDITIONS OR CHANGES WHICH ARE SET FORTH HEREIN, IS ACCEPTED AS TO ITEMS: SEE SCHEDULE							
30a. SIGNATURE OF OFFEROR/CONTRACTOR (b) (6)				31a. UNITED STATES OF AMERICA (SIGNATURE OF CONTRACTING OFFICER) (b) (6)							
30b. NAME AND TITLE OF SIGNER (TYPE OR PRINT) (b) (6)		30c. DATE SIGNED 08/17/20		31b. NAME OF CONTRACTING OFFICER (TYPE OR PRINT) (b) (6) CONTRACTING OFFICER TEL: (b) (6) EMAIL: (b) (6)				31c. DATE SIGNED 17-Aug-2020			

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CERTAIN CONFIDENTIAL PORTIONS OF THIS EXHIBIT HAVE BEEN OMITTED AND REPLACED WITH "[***]". SUCH IDENTIFIED INFORMATION HAS BEEN EXCLUDED FROM THIS EXHIBIT BECAUSE IT IS (I) NOT MATERIAL AND (II) WOULD LIKELY CAUSE COMPETITIVE HARM TO THE COMPANY IF DISCLOSED

AMENDMENT OF SOLICITATION/MODIFICATION OF CONTRACT			1. CONTRACT ID CODE		PAGE OF PAGES 113			
2. AMENDMENT/MODIFICATION NO. P00008		3. EFFECTIVE DATE See Block 16C		4. REQUISITION/PURCHASE REQ. NO. OS273940		5. PROJECT NO.(If applicable)		
6. ISSUED BY ASPR-BARDA 200 Independence Ave., S.W. Room 640-G Washington DC 20201 CODE		ASPR-BARDA		7. ADMINISTERED BY (If other than item 6) US DEPT OF HEALTH & HUMAN SERVICES ASST SEC OF PREPAREDNESS & RESPONSE ACQ MANAGEMENT, CONTRACTS, & GRANTS O'NEILL HOUSE OFFICE BUILDING Washington DC 20515 CODE			ASPR-BARDA02	
8. NAME AND ADDRESS OF CONTRACTOR (No., Street, County, State and Zip Code) MODERNAUS, INC. [***] 200 TECHNOLOGY SQ CAMBRIDGE MA 02139-3578 CODE 1492235				FACILITY CODE				
				11. THIS ITEM ONLY APPLIES TO AMENDMENTS OF SOLICITATIONS				
				The above numbered solicitation is amended as set forth in Item 14. The hour and date specified for receipt of Offer is extended, is not extended. Offer must acknowledge receipt of this amendment prior to the hour and date specified in the solicitation or as amended by one of the following methods: (a) By completing Items 8 and 15, and returning _____ copies of the amendment; (b) By acknowledging receipt of this amendment on each copy of the offer submitted; or (c) By separate letter or telegram which includes a reference to the solicitation and amendment numbers. FAILURE OF YOUR ACKNOWLEDGMENT TO BE RECEIVED AT THE PLACE DESIGNATED FOR THE RECEIPT OF OFFERS PRIOR TO THE HOUR AND DATE SPECIFIED MAY RESULT IN REJECTION OF YOUR OFFER. If by virtue of this amendment you desire to change an offer already submitted, such change may be made by telegram or letter, provided each telegram or letter makes reference to the solicitation and this amendment, and is received prior to the opening hour and date specified.				
				12. ACCOUNTING AND APPROPRIATION DATA (If required) See Schedule Net Increase: \$236,364,615.00				
13. THIS ITEM APPLIES ONLY TO MODIFICATIONS OF CONTRACTS/ORDERS. IT MODIFIES THE CONTRACT/ORDER NO. AS DESCRIBED IN ITEM 14.								
A. THIS CHANGE ORDER IS ISSUED PURSUANT TO: (Specify authority) THE CHANGES SET FORTH IN ITEM 14 ARE MADE IN THE CONTRACT ORDER NO. IN ITEM 10A.								
B. THE ABOVE NUMBERED CONTRACT/ORDER IS MODIFIED TO REFLECT THE ADMINISTRATIVE CHANGES (such as changes in paying office, appropriation date, etc.) SET FORTH IN ITEM 14, PURSUANT TO THE AUTHORITY OF FAR 43.103(B).								
X C. THIS SUPPLEMENTAL AGREEMENT IS ENTERED INTO PURSUANT TO AUTHORITY OF: FAR 52.243- 2 Alternate 1 (APR 1984) Changes - Cost-Reimbursement								
D. OTHER (Specify type of modification and authority)								
E. IMPORTANT: Contractor is not, is required to sign this document and return 1 copies to the issuing office.								
14. DESCRIPTION OF AMENDMENT/MODIFICATION (Organized by UCF section headings, including solicitation/contract subject matter where feasible.) Tax ID Number: 27-0226313 DUNS Number: 069723520 This contract (75A50120C00034 - Moderna COVID-19 Vaccine)was awarded under P.A.A. 18-100-SOL-00003 - Development of an mRNA Vaccine for SARS-CoV-2								

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8. NAME AND ADDRESS OF CONTRACTOR (No., Street, County, State and Zip Code) MODERNAUS, INC. [***] 200 TECHNOLOGY SQ CAMBRIDGE MA 02139-3578			9A. AMENDMENT OF SOLICITATION NO.
			9B. DATED (SEE ITEM 11)
		X	10A. MOD. OF CONTRACT/ORDER NO. 75A50120C00034
		X	10B. DATED (SEE ITEM 13) 04/03/2020
CODE 1492235		FACILITY CODE	
11. THIS ITEM ONLY APPLIES TO AMENDMENTS OF SOLICITATIONS			
The above numbered solicitation is amended as set forth in Item 14. The hour and date specified for receipt of Offer is extended, is not extended. Offer must acknowledge receipt of this amendment prior to the hour and date specified in the solicitation or as amended by one of the following methods: (a) By completing Items 8 and 15, and returning _____ copies of the amendment; (b) By acknowledging receipt of this amendment on each copy of the offer submitted; or (c) By separate letter or telegram which includes a reference to the solicitation and amendment numbers. FAILURE OF YOUR ACKNOWLEDGMENT TO BE RECEIVED AT THE PLACE DESIGNATED FOR THE RECEIPT OF OFFERS PRIOR TO THE HOUR AND DATE SPECIFIED MAY RESULT IN REJECTION OF YOUR OFFER. If by virtue of this amendment you desire to change an offer already submitted, such change may be made by telegram or letter, provided each telegram or letter makes reference to the solicitation and this amendment, and is received prior to the opening hour and date specified.			
12. ACCOUNTING AND APPROPRIATION DATA (If required) See Schedule Net Increase: \$236,364,615.00			
13. THIS ITEM APPLIES ONLY TO MODIFICATIONS OF CONTRACTS/ORDERS. IT MODIFIES THE CONTRACT/ORDER NO. AS DESCRIBED IN ITEM 14.			
	A. THIS CHANGE ORDER IS ISSUED PURSUANT TO: (Specify authority) THE CHANGES SET FORTH IN ITEM 14 ARE MADE IN THE CONTRACT ORDER NO. IN ITEM 10A.		
	B. THE ABOVE NUMBERED CONTRACT/ORDER IS MODIFIED TO REFLECT THE ADMINISTRATIVE CHANGES (such as changes in paying office, appropriation date, etc.) SET FORTH IN ITEM 14, PURSUANT TO THE AUTHORITY OF FAR 43.103(B).		
X	C. THIS SUPPLEMENTAL AGREEMENT IS ENTERED INTO PURSUANT TO AUTHORITY OF: FAR 52.243- 2 Alternate 1 (APR 1984) Changes - Cost-Reimbursement		
	D. OTHER (Specify type of modification and authority)		
E. IMPORTANT: Contractor is not, is required to sign this document and return <u>1</u> copies to the issuing office.			
14. DESCRIPTION OF AMENDMENT/MODIFICATION (Organized by UCF section headings, including solicitation/contract subject matter where feasible.) Tax ID Number: 27-0226313 DUNS Number: 069723520 This contract (75A50120C00034 - Moderna COVID-19 Vaccine)was awarded under BAA-18-100-SOL-00003 - Development of an mRNA Vaccine for SARS-CoV-2. The purpose of this modification is to support the additional scope of the Clinical Development Plan (CLIN 0002)which includes increases the P301(Efficacy)(WBS 1.4.3.1); Clinical(FTEs and digital clinical system)(WBS 1.4);Biologics License Application BLA (WBS 1.5.2) and Pharmacovigilance (supporting EUA) (WBS 1.5.3.1). The obligated amount of CLIN 0002 is increased from \$961,387,795 by \$236,364,615 to Continued ... Except as provided herein, all terms and conditions of the document referenced in Item 9A or 10A, as heretofore changed, remains unchanged and in full force and effect.			
15A. NAME AND TITLE OF SIGNER (Type or print) Stephane Bancel, CEO		16A. NAME AND TITLE OF CONTRACTING OFFICER (Type or print) [***]	
15B. CONTRACTOR/OFFEROR /s/ Stephane Bancel _____ (Signature of person authorized to sign)	15C. DATE SIGNED	16B. UNITED STATES OF AMERICA BY_____ (Signature of Contracting Officer)	16C. DATE SIGNED 04/18/2021

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CONTINUATION SHEET		Reference No. of Document Being Continued 75A50120C00034/P00008		PAGE 2	OF 11	
NAME OF OFFEROR OR CONTRACTOR MODERNATX, INC. 1492235						
Item No. (A)	Supplies/Services (B)	Quantity (C)	Unit (D)	Unit Price (E)	Amount (F)	
2	\$1,197,752,410.					
	CLIN 0002 is the only CLIN changed by the issuance of this modification. CLIN 0002 remains cost plus fixed fee (CPFF). Fee was not applied to the additional scope.					
				Prior Contract Value	Additional Funding	Revised Contract Value
	CLIN 0001	\$ 3,212,541	\$ -		\$ 3,212,541	
	CLIN 0002	\$ 961,387,795	\$ 236,364,615		\$ 1,197,752,410	
	CLIN 0003	\$ 53,000,000	\$ -		\$ 53,000,000	
	Total	\$ 1,017,600,336	\$ 236,364,615		\$ 1,253,964,951	
	All other contract terms and conditions remain unchanged.					
	Period of Performance: 04/03/2020 to 08/31/2023					
	Change Item 2 to read as follows(amount shown is the obligated amount):					
	Base CLIN 0002 - Development of mRNA vaccine to BLA					236,364,615.00
	Accounting Info:					
	2020.199COV1.25103 Appr. Yr.: 2020 CAN: 199COV1 Object Class:				25103	
	Funded: \$0.00					
	Accounting Info:					
2020.199C014.25103 Appr. Yr.: 2020 CAN: 199C014 Object Class:				25103		
Funded: \$0.00						
Accounting Info:						
2021.199C035.25103 Appr. Yr.: 2021 CAN: 199C035 Object Class:				25103		
Funded: \$0.00						
Accounting Info:						
2021.199C035.25103 Appr. Yr.: 2021 CAN: 199C035 Object Class:				25103		
Funded: \$236,364,615.00						

Assess Disease Enhancement (WBS 1.3.3.1)

The CoV spike protein expressed by the mRNA-1273 vaccine is stabilized in the prefusion conformation which should be optimal for inducing high quality antibody responses with low binding antibody to neutralizing antibody ratios. mRNA delivery and induction of CD8 T cells and Th1 CD4 T cells will avoid Th2-biased responses. The SARS-CoV-2 S protein expressed by the mRNA-1273 vaccine is stabilized in the pre-fusion conformation which should be optimal for inducing high functional antibody responses with low binding antibody to neutralizing antibody ratios, as it has been seen in RSV DS-Cav1 clinical trials and 2P-stabilized CoV S animal studies. In addition, mRNA vaccines induce Th1 skewed response as has been evident in several pre-clinical and clinical vaccine programs at Moderna, including pandemic flu and CMV (PMID 28457665, 29456015). By expressing pre-fusion SARS-CoV-2 S delivered with mRNA we should induce CD8 T cells and Th1-biased CD4 T cell responses as shown in both human, NHP, and murine studies, thus avoiding a Th2- biased response.

We plan to perform studies in mouse and NHPs to assess the theoretical risk of vaccine induced disease enhancement triggered by CoV infection following vaccination with imRNA-1273. [***]

[***]

Ralph Baric is also developing a human ACE-2 transgenic mouse model, resulting in viremia and lung pathology upon wild-type SARS-CoV-2 infection. This model should facilitate evaluation of wild-type SARS- CoV-2 virus and will also be used to evaluation protection from mRNA-1273 vaccination. This model is however still under development and data are unlikely to become available before June/ July 2020.

Finally, Vincent Munster (NIH/NIAID) has developed a Rhesus macaque model of SARS-CoV infection. After challenge animals get sick but infection is not lethal. Decreased respiration and irregular breathing, weight loss, fever spike at day 1 and evidence of pneumonia are all observed. In addition, hematological evidence of disease is seen, as well as viremia and shedding in nose, throat, and rectum up to day 10. Unlike what is observed clinically a high challenge dose of virus is required, and animals recover without intervention. Animals will be immunized with limiting doses of mRNA-1273 to allow breakthrough infection and endpoints relevant for disease enhancement will be collected. Results from these challenge studies may become available by end of June 2020.

Moderna's SEC filing of RALPH BARIC and the Vaccine

